Lesson of the Week

Secretion of antidiuretic hormone in hyponatraemia: not always "inappropriate"

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Severe hyponatraemia may occur in Addison's disease in the absence of other clinical features.[1] Enhanced secretion of antidiuretic hormone is a prominent feature of adrenal insufficiency and may in large part be responsible for the hyponatraemia seen in this condition.[2] In the original article describing the syndrome of inappropriate secretion of antidiuretic hormone the authors emphasised that this diagnosis should not be made until impaired adrenal function had been excluded.[3] The development of more refined assays for antidiuretic hormone has not changed this dictum, which obtains even when concentrations of the hormone appear grossly inappropriate for the degree of hyponatraemia.

A raised antidiuretic hormone concentration may be a feature of adrenal insufficiency; hence "inappropriate" secretion of antidiuretic hormone should never be diagnosed in a patient with hyponatraemia until impaired adrenal function has been definitely excluded

Case history

A 59 year old civil servant was brought to the casualty department by his wife, who described a two month history of malaise, fatigue, and weight loss, with several episodes of night sweats in the preceding two weeks. He had become drowsy, aggressive, and confused in the three days before admission. There was no history of tuberculosis and he had no respiratory symptoms or symptoms suggestive of a focal intracranial lesion. He smoked 20 cigarettes a day.

On examination he was unwell, drowsy, and disorientated. Temperature was 36°C, pulse 110/min, and blood pressure 110/70 mmHg lying; he was unable to stand for an erect measurement. There was no clubbing or pigmentation, nor were there any focal neurological signs. Results of initial investigations included the following: haemoglobin concentration 13·1 g/dl; white cell count $6{\cdot}5\times10^9$/l; erythrocyte sedimentation rate 95 mm in first hour; plasma sodium concentration 103 mmol (mEq)/l, potassium concentration 4·8 mmol (mEq)/l, urea concentration 5·5 mmol/l (33 mg/100 ml), and osmolality 227 mmol (mosmol)/kg; and urine osmolality 680 mmol/kg. Chest x ray appearances were initially interpreted as suggesting an isolated lesion in the right upper zone. A provisional diagnosis of inappropriate secretion of antidiuretic hormone due to carcinoma of the bronchus was made, water restriction instituted, and the patient referred to the respiratory physicians. Review of a series of chest radiographs showed development of definite miliary shadowing. Bronchial lavage and transbronchial biopsy showed nothing abnormal but a liver biopsy sample contained several giant cell granulomas highly suggestive of tuberculosis. Other relevant results included a normal CT scan of the head, normal results of lumbar puncture, normal renal function, disturbed liver function values (bilirubin concentration 23 μmol/l (1·3 mg/100 ml); aspartate transaminase activity 104 IU/l), negative Kveim and Mantoux test results, and serum thyroxine concentration 126 nmol/l (9·8 μg/100 ml). The antidiuretic hormone concentration measured when the serum osmolality was 230 mmol/kg was 5·1 pmol/l, which was grossly raised for the degree of hyponatraemia (normal range 1·0-3·0 pmol/l at normal serum osmolality).

After bronchoscopy he had an episode of severe hypotension, not associated with blood loss, which responded to oxygen, hypertonic saline, and hydrocortisone. Before the results of biopsy were available he began quadruple antituberculous treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol. Steroids were continued by mouth and fluid restriction maintained. He showed rapid clinical improvement and his sedimentation rate and serum osmolality returned to normal. He was discharged from hospital.

Six weeks later, having discontinued steroids 10 days previously, he was seen in the outpatient department and was unwell, fatigued, and nauseated. He had pronounced buccal and palmar crease pigmentation and his blood pressure was 100/65 mm Hg lying and 80/40 mm Hg standing. Serum sodium concentration was 120 mmol/l and serum osmolality 263 mmol/kg. A short tetracosactrin (Synacthen) test confirmed adrenal insufficiency: time zero (250 μg tetracosactrin intramuscularly), cortisol concentration 332 nmol/l (12·0 μg/100 ml); at 30 minutes, cortisol concentration 340 nmol/l (12·3 μg/100 ml). The adrenocorticotrophic hormone concentration was raised at 197 ng/l, confirming a primary adrenal deficit. The long tetracosactrin test (1 mg depot tetracosactrin intramuscularly at time zero) confirmed this (table).

Results of long tetracosactrin (Synacthen) test (1 mg depot preparation intramuscularly at time zero). Values are serum cortisol concentrations (nmol/l) at stated times after injection

	Time (hours)				
	0	2	4	8	24
Serum cortisol	314	191	266	247	228
Normal range	200-700	900-1200	1000-1350	1200-1400	950-1200

Conversion: SI to traditional units—Cortisol: 1nmol/l=0·04 μg/100 ml.

Adrenal autoantibodies were not detected and CT scan of the adrenals showed enlarged, irregular glands characteristic of tuberculous destruction. Hydrocortisone was reinstituted as replacement therapy. As rifampicin may have profound effects on steroid metabolism a suitable dose was chosen on the basis of serial cortisol measurements. Fludrocortisone 0·1 mg daily with hydrocortisone 40 mg daily in three divided doses was found to give the best clinical result and hormonal profile. On this regimen he showed rapid clinical and biochemical improvement and remained well.

Discussion

The availability of a sensitive, specific immunoassay for antidiuretic hormone has led to an improved understanding of hypoosmolar states. In particular, the list of causes of inappropriate secretion of antidiuretic hormone continues to grow. There is a

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danger, however, that Addison's disease may be neglected as a diagnostic possibility, especially when pigmentation is not a feature on presentation, as in this case.

The pathophysiology of hyponatraemia in adrenal insufficiency is imperfectly understood.[2-4] There is little doubt, however, that it includes disordered secretion of antidiuretic hormone.[5] That this is not solely due to the response of the hormone to volume depletion was shown by the persistence of antidiuretic hormone secretion in the face of hyponatraemia in volume repleted adrenalectomised rats.[6] Ahmed *et al* postulated a direct effect of cortisol deficiency on the hypothalamus which served to potentiate the response to other stimuli.[2] In a sense, therefore, Addison's disease may be considered as merely another cause of "inappropriate" secretion of antidiuretic hormone, although the clinical importance of differentiating them is plainly critical. There have been no systematic studies of antidiuretic hormone concentrations in Addison's disease since the development of a precise immunoassay. The one other reported case was remarkably similar to ours in many respects, including the clinical presentation, tuberculous aetiology, degree of hyponatraemia, and magnitude of the rise in antidiuretic hormone concentration.[7] As this is only the second such case to be reported it is impossible to say whether tuberculous Addison's disease is more likely to result in this metabolic disturbance than is autoimmune adrenalitis. Ectopic production of antidiuretic hormone has been shown in lung affected by chronic caseous tuberculosis, and it is therefore possible that Addison's disease and ectopic production of antidiuretic hormone coexisted in these patients. Such ectopic hormone production, however, has never been shown in miliary disease. Although we failed to grow the acid fast bacillus, the radiological and pathological evidence and the rapid improvement in clinical state and markers of inflammation secure the primary diagnosis.

The patient described by Lever and Stansfield caused some alarm by suffering a relapse of hyponatraemia with raised antidiuretic hormone concentrations despite receiving replacement steroids. The authors were unable to account for this. Our experience and that of others, however, indicates that conventional replacement doses of steroids may not be adequate while the patient is taking rifampicin.[8] It is quite likely that the explanation for the relapse of hyponatraemia was simply inadequate steroid replacement. Although formal testing of adrenal function was not possible at presentation because of the prior administration of steroids, in retrospect it is possible to discern some clues to the presence of adrenal insufficiency. The slightly low blood pressure and the normal potassium and urea concentrations in the face of severe hypo-osmolality should perhaps have raised suspicion. Serum for cortisol estimation should have been reserved before hydrocortisone was given, despite the emergency nature of the treatment.

Further studies of antidiuretic hormone secretion in Addison's disease are necessary, but it remains vital to understand that in the investigation of hyponatraemia the finding of a raised antidiuretic hormone concentration does not exclude Addison's disease but may, in fact, represent a salient metabolic feature of this disease.

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For Debate . . .

Dexamethasone suppression test as a simple measure of stress?

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Abstract

Non-suppression of cortisol by dexamethasone has been described as a biological marker of a diagnostic subgroup of depressed patients. This paper presents the hypothesis that the degree of non-suppression is a variable that reflects the quantity of stress or distress experienced by the patient rather than relating to a specific diagnosis. Such a quantitative measure of stress would be valuable for research in general medicine as well as in psychiatry. Testing of this postulate should apply a more precise interpretation of endocrine principles than has been applied to the dexamethasone suppression test to date.

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Introduction

Serum cortisol concentrations may be raised by many factors causing stress or threats to homoeostasis.[1] Carroll claimed that though there is no consistent relation between corticosteroid concentrations and psychiatric conditions, a more dynamic test of the production of cortisol, the 1 mg dexamethasone suppression test, permits the delineation of a specific subgroup of depressed patients exhibiting melancholia.[2] The initial enthusiasm for this suggestion has been gradually tempered by caution.[3-5] The specificity of the dexamethasone suppression test has been questioned particularly in clinical circumstances in which diagnostic discrimination